

**REMARKS**

Upon entry of the present amendment, claims 44, 46, 48-50, 52-53, 55-57, 59-62, and 64-69 will be pending in this application and presented for examination. Claims 44, 46, 48, 52, 53, 55, 59, 62, and 64 have been amended. Claims 45, 47, 51, 54, 58 and 63 have been canceled without prejudice. Claims 67-69 are newly presented.

At the outset, Applicants and their representative wish to thank Examiners Kam and Low for the telephonic interview held on July 30, 2003. During this interview, a number of issues were clarified and an amendment was proposed that have helped the Applicants to more fully address the concerns of the Examiners. Applicants thank Examiners Kam and Low for their time and the courtesy of extending the interview.

Reconsideration of the application is respectfully requested in view of the amendments to the claims and the following remarks. Applicants believe no new matter is present in this or any other portion of the present amendment.

**I. SUPPORT FOR THE AMENDMENTS AND NEW CLAIMS**

The amendments to the claims and new claims find support throughout the specification as filed. More particularly, support for the terms in the phrase "specific selected protein" is found, *inter alia*, on page 2, lines 4-6, where it is described that the specific protein is selected from a group of related proteins that are expressed in different tissue types. Support for the term "member of a homologous protein series" is found, *inter alia*, on page 2, lines 7-16 and page 6, lines 1-10. Support for the phrase "binds either electrostatically or covalently" is found, *inter alia*, on page 12, lines 1-4. Support for the use of the terms "first binding site" and "second binding site" is found, *inter alia*, on Figure 1C, which depicts that an anchor group, e.g. methanethiosulfonate, binds to the first binding site on the protein and a drug, e.g. benzocaine, binds to a second binding site on the protein. Support for the terms "ion channel and membrane receptor" is found, *inter alia*, on page 6, lines 26-27 and in claim 48, respectively. Support for the phrase "binds non-specifically for members of a homologous protein series" is found, *inter alia*, on page 2, lines 4-6 and lines 17-18. Support for the compounds recited in claim 68 is

found, *inter alia*, in Figure 2. Support for the term "calcium ion channel protein" and "cardiac muscle tissue" is found, *inter alia*, on page 2, lines 15-16. As such, Applicants respectfully request that the amendments and new claims be entered.

## **II. FORMALITIES**

The Examiner requested clean copies of Figure 5A-5D and Figure 8. Applicants have complied with the Examiner's request by submitted the required clean copies of the drawings. Accordingly, Applicants respectfully request that all rejections to the drawings be withdrawn.

## **III. CLAIM OBJECTIONS**

The Examiner has objected to claims 46, 48, 49, 50, 53, 55-57, 62, and 64-66 as allegedly being drawn to non-elected inventions. The Examiner alleges that the members of the group recited for a drug, a target homologous protein, and an anchoring moiety, do not (1) share a common utility or (2) share a substantial structural feature disclosed as being essential to that utility as set forth under MPEP § 803.02.

In an earnest effort to advance the prosecution of the present application, Applicants have amended claims 46, 53 and 62 to set forth a list of small organic molecule drugs. Further, the specific selected proteins recited in claims 48, 55, and 64 share the common utility as therapeutic protein targets to which compounds of formula A-L-D bind with affinity. Furthermore, the proteins share a structural feature of being members of groups of homologous proteins. A homologous protein is a protein that shares a highly conserved functional binding site and is expressed in distinct tissue types (*see*, page 2, lines 7-14). Claims 49-50, 56-57, 65-66 are drawn to an anchoring moiety. The "anchoring moieties" recited share the common utility as a moiety that binds covalently or non-covalently to a binding site on a specific selected protein. Moreover, the anchoring moieties all share the common structural feature of having a chemical functional group that can react with a specific selected protein that forms a covalent bond at a

first binding site. As such, Applicants maintain that the claims as amended do meet the unity of invention requirement, and respectfully request that the rejection be withdrawn.

**IV. REJECTION UNDER 35 U.S.C § 112**

The Examiner alleges that claims 44-58 are indefinite because the claims indicates that a drug binds at a preselected target site and it also indicates that the drug is linked to an anchoring moiety that is specific for the chemically reactive group at the preselected target site. The Examiner alleges that the nature of the binding to the preselected target site is unclear. In particular, it is alleged that it is unclear whether the drug binds at the preselected target site via the anchoring group, or if it binds to the same preselected target site as the anchoring group.

In response, claims 45, 47, 51, 54, and 58 have been canceled without prejudice. Further, Applicants have amended independent claims 44 and 52 to clearly specify the nature of the binding of the compound A-L-D. Claims 44 and 52 now read as follows:

44. (Currently Amended) A method for targeting a drug to a specific selected protein, wherein the specific selected protein is a member of a homologous protein series selected from the group consisting of an ion channel and a membrane receptor, said method comprising:

contacting said specific selected protein with a compound having the formula

A-L-D

wherein:

A is an anchoring moiety that binds selectively, either covalently or electrostatically to a first binding site on said specific selected protein;

L is a linking group; and

D is a compound or drug that binds to a second binding site on said specific selected protein, wherein said first binding site and said second binding site are distinct.

52. (Currently Amended) A method for identifying a compound of formula:

A-L-D

that binds a specific selected protein, and wherein the specific selected protein is a member of a homologous protein series selected from the group consisting of ion channel and membrane receptor, said method comprising:

(a) providing a specific selected protein that comprises a first binding site and a second binding site on said specific selected protein;

(b) contacting said specific selected protein, with a compound, said compound comprising (1) A, wherein A is an anchoring moiety and (2) L, wherein L is a linking group, wherein said anchoring moiety binds specifically either covalently or electrostatically as a ligand to said first binding site on specific selected protein, thereby resulting in said anchoring moiety being attached to said specific selected protein;

(c) combining said specific selected protein from step (b) with one or more members of a library of drugs that are capable of covalently binding to said linking group, wherein at least one member of said library binds to a second binding site on said specific selected protein and forms a covalent bond with said linking group to form a specific selected protein conjugated to A-L-D, wherein D is at least one member of said library forming said covalent bond; and

(d) identifying said drug, D, that forms a covalent bond with said linking group.

Applicants have amended the claims to clearly indicate the presence of two distinct protein binding sites, the first site which binds to the anchor moiety and the second site which binds to the drug. In view of these amendments, Applicants believe that the independent claims 44 and 52 and dependent claims 46, 48-50, 53, and 55-57 are definite and respectfully request that the rejection be withdrawn.

The Examiner alleges that the use of the phrase "drug having an anchoring moiety" in claim 45 is indefinite because it is unclear whether the drug itself contains an anchoring moiety, or if it is linked to an anchoring moiety as stated in claim 44. Applicants have canceled claim 45 and respectfully submit that the rejection has been rendered moot. As such, Applicants respectfully request that the rejection be withdrawn.

The Examiner rejected claims 47, 54, and 63 as allegedly being indefinite because of the use of the term "said biological target molecule is on a protein". Applicants have canceled claims 47, 54, and 63 and respectfully submit that the rejection has been rendered moot. As such, Applicants respectfully request the rejection be withdrawn.

## **V. REJECTIONS UNDER 35 § U.S.C. § 102 AND 35 U.S.C. § 103**

The Examiner has rejected claims 44, 47 and 51 under 35 U.S.C. § 102(b) as allegedly being anticipated by, or alternatively under 35 U.S.C. § 103(a) as allegedly being

obvious in view of Greenfield *et al.* (EP 0398305). To the extent that the rejection is applicable to the amended set of claims, Applicants respectfully traverse the rejection.

The Examiner alleges that Greenfield *et al.* teach a method for delivering a drug conjugate consisting of anthracycline (a drug), which is attached to a cell reactive molecule such as an antibody, or a ligand of EGF (anchoring group), through a linker as is taught in the present invention.

Greenfield *et al.* teach that an anthracycline molecule is attached to a cell reactive molecule wherein the cell reactive molecule has specificity for a targeted site. However, the anthracycline molecule alone has no specificity for the targeted cells or tissue (*see*, EP0398305, page 9 lines 1-5).

In stark contrast, the present invention teaches a method wherein a compound of formula A-L-D contacts a specific selected protein in a manner wherein A, the anchoring group, binds specifically to a first binding site on a specific selected protein, and D, the drug, binds to a second binding site on the specific selected protein. Applicants have amended Claim 44 to recite that there are two distinct binding sites on the specific selected protein, one that is specific for the anchoring group and one that is specific for the drug. Greenfield simply does not teach or suggest the presence of a second binding site to which a drug can bind. Therefore, Greenfield does not teach or suggest the present invention. In view of the foregoing, Applicants believe that the Examiner's concerns are overcome and respectfully request the rejection(s) be withdrawn.

Furthermore, the Examiner has rejected claims 44, 47, 49-52, 54, and 56-58 under 35 U.S.C. § 102(b) as allegedly being anticipated by, or alternatively under 35 U.S.C. § 103(a) as allegedly being obvious in view of Pouletty *et al.* (WO 95/10302).

Pouletty *et al.* teach that a conjugate having an anchor and a physiologically active entity (a drug) wherein the anchor group binds to a long-lived blood component such as an erythrocyte in circulation. Pouletty *et al.* further teach that the physiologically active entity then binds to another molecular target which is **not** on the same blood component. The only purpose of the anchoring described in Pouletty *et al.* is to extend the half-life of drugs in the blood compartment (*see*, WO95/10302, Abstract, first line). Pouletty *et al.* do not teach that the binding of the anchor group facilitates the binding of the drug to the same target tissue or protein.

As such, Pouletty *et al.*, teaches a three component binding system: the drug conjugate, a blood component to which the anchor binds, and a target moiety to which the drug binds.

In stark contrast, the present invention teaches a method wherein a compound of formula A-L-D contacts a specific selected protein in a manner wherein A, the anchoring group, binds to a first binding site on a specific selected protein that is located on a specific tissue type. The drug, D, then binds to a second binding site on the **same** specific selected protein or tissue type. In contrast to the teaching of Pouletty *et al.*, the binding of the anchor group **does** facilitate the binding of the drug to the second binding site. For further clarification, Applicants have amended claims 44 and 52 to clearly recite that there are two distinct binding sites, one that is specific for the anchoring group and one that is specific for the drug.

Pouletty *et al.* simply do not teach or suggest that the drug binds to the same target tissue or protein as the anchor group. As such, Pouletty *et al.* do not teach or suggest the present invention. In view of the amendment to the independent claims 44 and 52, Applicants believe claims 44 and 52 and dependent claims 49-50, 53-54, 56-57 are not anticipated or made obvious in view of Pouletty *et al.*, and request the rejection be withdrawn.

## VI. REJECTION UNDER 35 U.S.C. § 102

The Examiner has rejected claims 59-62 under 35 U.S.C. § 102(e) as allegedly being anticipated by Fesik *et al.* (US Patent No. 5,989,827), stating that the present method does not clearly distinguish itself from Fesik. To the extent the rejection is applicable to the amended set of claims, Applicants respectfully traverse the rejection.

Fesik *et al.* teach a process for the design and identification of compounds that bind to a protein. This process comprises the steps of:

1. Identify a first ligand to the target biomolecule;
2. Identify a second ligand to the target biomolecule;
3. Form a ternary complex by binding both ligands to the target biomolecule;
4. Determine the three-dimensional structure of the ternary complex formed; and
5. Link the first and second ligands together to form the drug.

In this process, the two ligands are **identified separately**, and then linked only in the *step 5* of the process. Furthermore, Fesik teaches a method of identifying two ligand that each individually has specificity for the protein (*see*, column 2, lines 43-46), and then linking these two ligands together to form a drug.

In stark contrast, the instant invention teaches a method for in which the anchoring group and the drug are **identified together**. The method involves contacting a compound of formula:

A-L-D

to the specific selected protein, wherein A is an anchoring moiety that binds specifically to first binding site on a specific selected protein; L is a linking group; and D is a drug that binds to the second binding site on the specific selected protein. Therefore, in contrast to Fesik *et al.*, which teaches first identifying two separate ligands and then linking them together, the instant invention teaches a method for identifying an **intact** compound of formula A-L-D to a specific selected protein.

In view of the amendments to the claims, Applicants submit that the instant invention is not anticipated by Fesik *et al.* Accordingly, Applicants respectfully request that the rejection be withdrawn.

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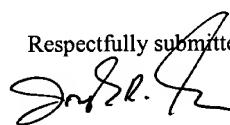
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**VII. CONCLUSION**

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 925-472-5000.

Respectfully submitted,



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